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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,523	01/18/2006	Yusuke Nakamura	082368-003700US	6149

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EXAMINER	
AEDER, SEAN E	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
31 DAYS	12/27/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,523	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 3/28/06.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-26 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

It is noted that the claims of the instant application have been determined to include linking claims. Claim 1 link(s) inventions I-III, as set forth below. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/ are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

I. Claims 2-8, as specifically drawn to a method of diagnosing a predisposition to developing metastatic colorectal cancer comprising determining a level of expression of metastasis-associated gene in a patient wherein said level of expression is determined by detecting mRNA of the metastasis-associated gene, classified in class 435, subclass 6.

II. Claims 2-4, 7, and 8, as specifically drawn to a method of diagnosing a predisposition to developing metastatic colorectal cancer comprising determining a level of expression of metastasis-associated gene in a patient wherein said level of expression is determined by detecting protein encoded by the metastasis-associated gene, classified in class 435, subclass 7.1.

III. Claims 2-4, 7, and 8, as specifically drawn to a method of diagnosing a predisposition to developing metastatic colorectal cancer comprising determining a level of expression of metastasis-associated gene in a patient wherein said level of expression is determined by detecting the biological activity of a protein encoded by the metastasis-associated gene, classified in class 435, subclass 4.

IV. Claim 9, drawn to a primary colorectal cancer reference expression profile comprising a pattern of gene expression of two or more genes, classified in class 702, subclass 19.

(Note: Upon election of group IV, Applicant must further select a single group consisting of up to 10 genes of MLXs 1-163. It is noted that each group of genes represent a single invention and NOT a species.)

V. Claims 10, 17, and 23, as specifically drawn to a method of screening a compound comprising contacting a test compound with a polypeptide and detecting the binding activity between said polypeptide and said test compound and a method of administering said compound, classified in class 435, subclass 4.

VI. Claims 11, 17, and 23, as specifically drawn to a method of screening a compound comprising contacting a test compound with a polypeptide and detecting the biological activity of said polypeptide and a method of administering said compound, classified in class 435, subclass 4.

VII. Claims 12-14, 17, and 23, as specifically drawn to a method of screening a compound comprising contacting a test compound with a cell expressing one or more marker genes, or a cells comprising a regulatory region of a marker gene, and selecting a compound that reduces the expression level of one or more marker genes, or a reporter gene controlled by said regulatory region, and a method of administering said compound, classified in class 435, subclass 6.

(Note: Upon election of group VII, Applicant must further select either one or a group consisting up to 10 marker genes of MLXs 1-

163. It is noted that a cell comprising a single marker genes or up to 10 marker genes represents a single invention and NOT a species.)

VIII. Claims 15, 16, and 26, as specifically drawn to MLX encoding polynucleotides, classified in class 536, subclass 23.1.
(Note: Upon election of group VIII, Applicant must further select either one or a group consisting of up to 10 nucleic acid sequences of MLXs 1-163. It is noted that this selection represents a single invention and NOT a species.)

IX. Claim 18, drawn to a method for treating colorectal cancer or preventing metastasis of colorectal cancer comprising administering antisense nucleic acids(s) or small interference RNA(s), classified in class 514, subclass 44.
(Note: Upon election of group IX, Applicant must further select either one or a group consisting of up to 10 nucleic acid sequences of MLXs 1-163. It is noted that this selection represents a single invention and NOT a species.)

X. Claim 19, drawn to a method for treating colorectal cancer or preventing metastasis of colorectal cancer comprising administering antibody(ies), classified in class 424, subclass 130.1.

(Note: Upon election of group X, Applicant must further select either one or a group of antibodies that specifically bind up to 10 polypeptides encoded by nucleic acid sequences of MLXs 1-163. It is noted that this selection represents a single invention and NOT a species.)

XI. Claim 20-22, as specifically drawn to treating cells with and administering polypeptide(s) of MLXs, classified in class 424, subclass 193.1.
(Note: Upon election of group XI, Applicant must further select either one or a group of up to 10 polypeptides encoded by MLXs 1-163. It is noted that this selection represents a single invention and NOT a species.)

XII. Claim 20-22, as specifically drawn to treating cells with or administering polynucleotide(s) of MLXs, classified in class 514, subclass 44.
(Note: Upon election of group XII, Applicant must further select either one or a group of up to 10 polynucleotides of MLXs 1-163. It is noted that this selection represents a single invention and NOT a species.)

XIII. Claim 24, drawn to compositions comprising antisense nucleic acids or small interfering RNAs, classified in class 536, subclass 24.5.

(Note: Upon election of group XIII, Applicant must further select either one or a group of up to 10 polynucleotides of MLXs 1-163. It is noted that this selection represents a single invention and NOT a species.)

XIV. Claim 25, drawn to compositions comprising an antibody, classified in class 530, subclass 387.1.

XV. Claim 26, drawn to compositions comprising a polypeptide, classified in class 530, subclass 350.

The inventions are distinct, each from the other because of the following reasons:

The Inventions of groups IV, VIII, and XIII-XV represent separate and distinct products which are made by materially different methods, and are used in materially different methods which have different modes of operation, different functions and different effects. Group IV is drawn to an expression profile, group VIII is drawn to MLX encoding polynucleotides, group XIII is drawn to antisense nucleic acids and small interfering RNAs, group XIV is drawn to antibodies, and group XV is drawn to polypeptides encoded by MLXs.

The DNA of group VIII is related to the protein of group XV by virtue of the fact that the DNA codes for the protein. The DNA molecule has utility for the recombinant production of the protein in a host cell. Although the DNA and the protein are related,

since the DNA encodes the specifically claimed protein, they are distinct inventions because the protein product can be made by other and materially distinct processes, such as purification from the natural source. Further, DNA can be used for processes other than the production of protein, such as nucleic acid hybridization assays.

Furthermore, searching the inventions of groups VIII and XV together would impose a serious search burden. In the instant case, the search of the polypeptides and polynucleotides are not coextensive. The inventions of groups VIII and XV have a separate status in the art as shown by their different classifications. In cases such as this one where descriptive sequence information is provided, the sequences are searched in appropriate database. There is search burden also in the non-patent literature. Prior to the concomitant isolation and expression of the sequences of interest there may be journal articles devoted solely to polypeptides which would not have described the polynucleotide. Similarly, there may have been "classical" genetics papers which had no knowledge of the polypeptide but spoke to the gene. Searching, therefore is not coextensive. A search of the nucleic acid molecules of group VIII would require an oligonucleotide search, which is not likely to result in relevant art with respect to the polypeptide of group XV. As such, it would be burdensome to search the inventions of groups VIII and XV.

The polypeptide of group XV and the antibody of group XIV are patentably distinct for the following reasons:

While the inventions of both group XV and group XIV are polypeptides, in this instance the polypeptide of group XV represents a purified polypeptide encoded by a

MLX, whereas the polypeptide of group XIV encompasses antibodies including IgG which comprises 2 heavy and 2 light chains containing constant and variable regions, and including framework regions which act as a scaffold for the 6 complementarily determining regions (CDR) that function to bind an epitope. Thus the polypeptide of group XV and the antibody of group XIV are structurally distinct molecules; any relationship between a polypeptide of group XV and an antibody of group XIV is dependent upon the correlation between the scope of the polypeptide that the antibody binds and the scope of the antibodies that would be generated upon immunization with the polypeptide. In this case, the polypeptide of group XV contains potentially hundreds of regions to which an antibody may bind, whereas the antibody of group XIV is defined in terms of its binding specificity to a small structure. Furthermore, searching the inventions of group XV and group XIV would impose a serious search burden. The inventions have separate status in the art as shown by their different classifications. A polypeptide and an antibody which binds to the polypeptide require different searches. An amino acid sequence search of the full-length protein is necessary for a determination of novelty and unobviousness of the protein. However, such a search is not required to identify the antibody of group XIV. Furthermore, antibody which binds to an epitope of a polypeptide of group XV may be known even if a polypeptide of group XV is novel. In addition, the technical literature search for the polypeptide of group XV and the antibody of group XIV are not coextensive, e.g., antibodies may be characterized in the technical literature prior to discovery of or sequence of their binding target.

The polynucleotide of group VIII and the antibody of group XIV are patentably distinct for the following reasons:

The antibody of group XIV includes, for example, IgG molecules which comprise 2 heavy and 2 light chains containing constant and variable regions, and including framework regions which act as a scaffold for the 6 complementarily determining regions (CDRs). Polypeptides, such as the antibody of group XIV which are composed of amino acids, and polynucleotides, which are composed of nucleic acids, are structurally distinct molecules; any relationship between a polynucleotide and polypeptide is dependent upon the information provided by nucleic acid sequence open reading frame as it corresponds to the primary amino acid sequence of the encoded polypeptide. In the present claims, a polynucleotide of group VIII will not encode an antibody of group XIV, and the antibody of group XIV cannot be encoded by a polynucleotide of group VIII. Therefore, the antibody and polynucleotide are patentably distinct.

The antibody and polynucleotide inventions have a separate status in the art as shown by their different classifications. Furthermore, searching the inventions of group VIII and group XIV would impose a serious search burden since a search of the polynucleotides of group VIII would not be used to determine the patentability of any antibody of group XIV, and vice-versa.

The inventions of groups I-III, V-VII, and IX-XII are materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success. Groups I-III are drawn to

methods of diagnosing using different reagents and methods, group V-VII are drawn to methods of screening using different detection methods, IX-XII are drawn to methods of treating using different reagents. Each group would require different searches in the literature, in part, due to the different classifications of each group. Searching all the methods would be unduly burdensome because each search would require different searches in the literature that would not necessarily be co-extensive. Further, examining each method requires the consideration of different patentability issues.

Inventions I and VIII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the polynucleotides is group VIII can be used in the materially different process of gene therapy.

Inventions II and XIV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the antibody of group XIV can be used in the materially different process of immunotherapy.

Inventions V and XV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the

process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the polypeptide of group XV can be used in the materially different process of generating antibodies.

Inventions VI and XV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the polypeptide of group XV can be used in the materially different process of generating antibodies.

Inventions IX and XIII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the antisense and siRNA products of group XIII can be used in the materially different process of affinity chromatography.

Inventions X and XIV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially

different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the antibodies of group XIV can be used in the materially different process of detecting protein expression.

Inventions XI and XV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the polypeptides of group XV can be used in materially different processes of screening compounds.

Inventions VIII and XII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the polynucleotides of group VIII can be used in the materially different process of affinity chromatography.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required, restriction for examination purposes as indicated is proper.

Note:

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Species

Claims 1-8, 10, 11, 14, 17-19, and 23-26 are generic to a plurality of disclosed patentably distinct species of **metastasis-associated genes** comprising the following: MLX 1; MLX 2; MLX 3;....MLX 163 etc. The products of the above species represent separate and distinct molecules with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature essential to that utility.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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